



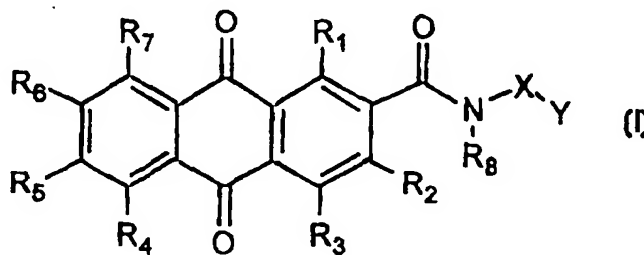
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(54) Title: N-AMINOALKYL-2-ANTHRAQUINONECARBOXAMIDES; NEW DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS

(57) Abstract

Disclosed are compounds of formula (I) or the pharmaceutically acceptable acid addition salts thereof wherein: R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are the same or different and represent hydrogen, halogen, alkyl, alkoxy, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -O₂CR', -NHCOR', -COR', -SO_mR', where R' is C₁-C₆alkyl and wherein m is 0, 1 or 2; or R₁, R₂, R₃, R₄, R₅, R₆, and R₇ independently represent -CONR'R'', or -NR'R'' where R' and R'' independently represent hydrogen or C₁-C₆alkyl; R₈ is hydrogen or lower alkyl; X represents an optionally substituted alkylene group; and Y represents a mono-, di- or trisubstituted cyclic amino group, which compounds are useful in the treatment of affective disorders such as schizophrenia, depression, Alzheimer's disease, movement disorders such as Parkinsonism and dystonia, and other disorders which respond to dopaminergic blockade such as substance abuse and obsessive compulsive disorders. Further, compounds of this invention may be useful in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents.



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**N-aminoalkyl-2-anthraquinonecarboxamides,
New Dopamine Receptor Subtype Specific Ligands**

BACKGROUND OF THE INVENTION

5 **Field of the invention**

This invention relates to anthraquinonecarboxamide derivatives which selectively bind to brain dopamine receptor subtypes. More specifically, it relates to N-Aminoalkylanthraquinonecarboxamide carboxamides and to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in the treatment or prevention of various neuropsychological disorders such as schizophrenia and other central nervous system diseases.

Description of the Related Art

15 The therapeutic effect of conventional antipsychotics, known as neuroleptics, is generally believed to be exerted through blockade of dopamine receptors. However, neuroleptics are frequently responsible for undesirable extrapyramidal side effects (EPS) and tardive dyskinesias, which are attributed to blockade of D₂ receptors in the striatal region of the brain. The dopamine D₃ receptor subtype has recently been identified (Sokoloff et al., Nature, 347, 146 (1990)). Its unique localization in limbic brain areas and its differential
20 recognition of various antipsychotics indicates that the D₃ receptor plays a significant role in the etiology of schizophrenia. Selective D₃ antagonists are thought to be effective antipsychotics free from the neurological side effects displayed by conventional neuroleptics.

U.S. Patent No. 5,395,835 discloses N-aminoalkyl-2-naphthalamides said to have affinity at dopamine D₃ receptors.

25 Murray et al., Bioorg. Med. Chem. Let. 5 219 (1995), describe 4-carboxamidobiphenyls said to have affinity at dopamine D₃ receptors.

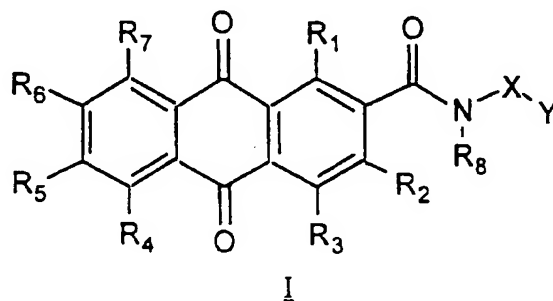
SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with dopamine receptor subtypes. Thus, the invention provides compounds of general Formula I useful in the treatment and/or prevention of various neuropsychological disorders. The invention also provides pharmaceutical compositions comprising compounds of Formula I.

Since dopamine D₃ receptors are concentrated in the limbic system (Taubes, Science, 265: 1034 (1994)) which controls cognition and emotion, compounds which interact with these receptors also have utility in the treatment of cognitive disorders. Such disorders include cognitive deficits which are a significant component of the negative symptoms (social withdrawal and unresponsiveness) of schizophrenia. Other disorders involving memory impairment or attention deficit disorders can also be treated with the compounds of this invention which interact specifically with the dopamine D₃ receptor subtype.

Furthermore, compounds of this invention may be useful in treatment of depression, memory-impairment or Alzheimer's disease by modulation of D₃ receptors which selectively exist in limbic area known to control emotion and cognitive functions. The compounds of the present invention are also useful for the treatment of other disorders which respond to dopaminergic blockade such as substance abuse (Caine and Koob, Science, 260: 1814 (1993)) and obsessive compulsive disorder (Goodman et al., Clin. Psychopharmacol., 7: 35 (1992)). The compounds of the invention interact with dopamine receptor subtypes resulting in the pharmacological activity of these compounds.

Accordingly, a broad embodiment of the invention is directed to a compound of Formula I:



or the pharmaceutically acceptable acid addition salts thereof wherein:

R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are the same or different and represent hydrogen, halogen, alkyl, alkoxy, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -O₂CR', -NHCOR', -COR', -SO_mR', where R' is C₁-C₆ alkyl and wherein m is 0, 1 or 2; or

R₁, R₂, R₃, R₄, R₅, R₆, and R₇ independently represent -CONR'R", or -NR'R" where R' and R" independently represent hydrogen or C₁-C₆ alkyl;

R₈ is hydrogen or lower alkyl;

X represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more alkyl groups having from 1 to 4 carbon atoms;

Y represents a cycloalkyl amino group.

10

Thus, the invention relates to the use of compounds of Formula I in the treatment and/or prevention of neuropsychochological disorders including, but not limited to, schizophrenia, Alzheimer's disease, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson-like motor disorders such as dystonia, and motion disorders and extrapyramidal side effects related to the use of neuroleptic agents.

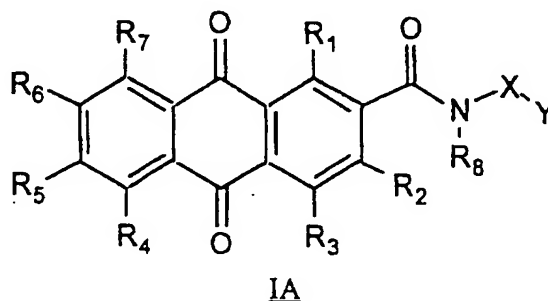
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DETAILED DESCRIPTION OF THE INVENTION

Compounds of the present invention demonstrate high affinity and selectivity in binding to the D₃ receptor subtype. Therefore, they are of use in treatment of schizophrenia, psychotic depression and mania. Other dopamine-mediated diseases such as Parkinsonism and tardive dyskinesias can be treated directly or indirectly by modulation of D₃ receptors.

The invention thus provides of such compounds and compositions useful in the treatment of affective disorders such as schizophrenia, depression, Alzheimer's disease and certain movement disorders such as Parkinsonism and dystonia. Compounds of this invention are also useful in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents. Further, the compounds of the present invention are useful for the treatment of other disorders which respond to dopaminergic blockade such as substance abuse and obsessive compulsive disorder.

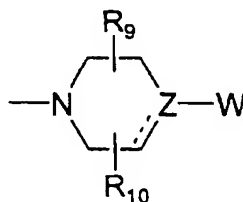
In addition to compounds of general Formula I described above, the invention encompasses compounds of Formula IA:



or the pharmaceutically acceptable acid addition salts thereof wherein:

X, R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are defined as above for Formula I; and

Y represents a cycloalkyl group of the formula:



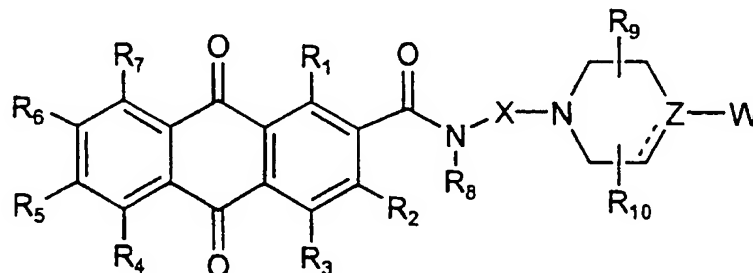
where R₉ and R₁₀ independently represent alkyl;

Z is nitrogen or carbon ; and

W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl, indenyl, or dihydroindenyl, preferably 4-(1,2-dihydro)indenyl, quinolinyl, pyridinyl, pyrimidyl, isoquinolinyl, benzofuranyl, benzothienyl; each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

Preferred compounds of formula IA include those where R₁-R₇ are hydrogen; R₈ is hydrogen, methyl, or ethyl; and X is alkylene of 3-5 carbon atoms.

In addition, the invention encompasses compounds of Formula IB:

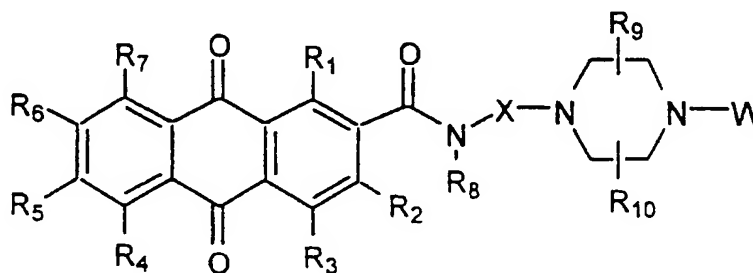


IB

wherein R₁-R₈, X, Z, W and R₉ and R₁₀ are as defined above for Formula I.

Preferred compounds of formula IB include those where R₈ is hydrogen, methyl, or ethyl, and X is alkylene of 3-5 carbon atoms. Particularly preferred compounds of Formula IB are those where R₈ is hydrogen and X is butylene, i.e., C₄ alkylene.

The invention further encompasses compounds of Formula II:



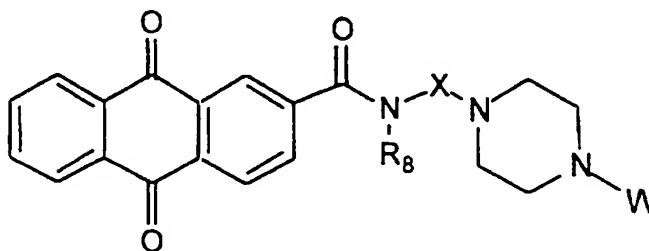
II

wherein R₈, X, Z, and W are as defined above for Formula I.

Preferred compounds of formula II include those where R₈ is hydrogen and X is alkylene of 3-5 carbon atoms.

In other preferred compounds of Formula II, R₈ is hydrogen and X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

The invention also encompasses compounds of Formula IIA:



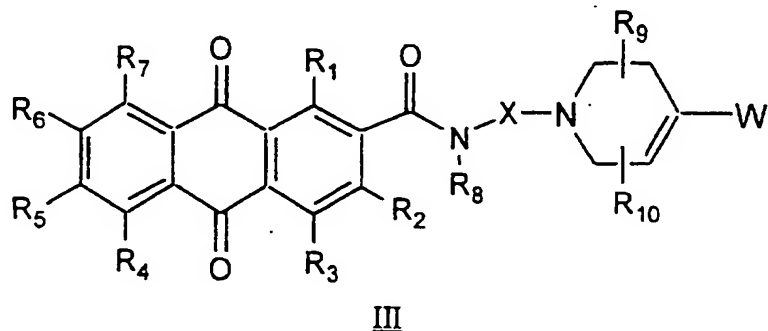
IIA

wherein R₈, X, and W are as defined above for Formula I.

Preferred compounds of formula IIA include those where R₈ is hydrogen, methyl, or ethyl, and X is alkylene of 3-5 carbon atoms.

In other preferred compounds of Formula IIA, R₈ is hydrogen and X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy. More preferred compounds of Formula IIA are those where R₈ is hydrogen; A is C₃₋₅ alkylene; and W is quinolinyl, isoquinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the group to the piperazine ring), the groups being independently selected from chloro, methyl, and methoxy. Particularly preferred compounds of Formula IIA are those where R₈ is hydrogen; A is C₄ alkylene; and W is naphthyl, 8-quinolinyl, or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the piperazine ring), the groups being independently selected from chloro, methyl, and methoxy.

In addition, the present invention provides compounds of Formula III:

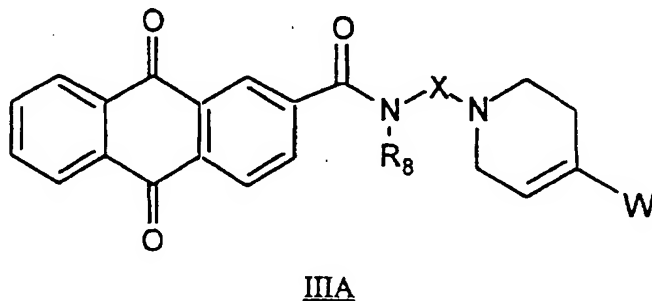


wherein R₁-R₁₀, X, and W are as defined above for Formula I.

5 Preferred compounds of formula III include those where R₈ is hydrogen and X is alkylene of 3-5 carbon atoms. Particularly preferred compounds of Formula III are those where R₈ is hydrogen, and X is butylene, i.e., C₄ alkylene.

In other preferred compounds of Formula III, R₈ is hydrogen, X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

The invention also encompasses compounds of Formula IIIA:



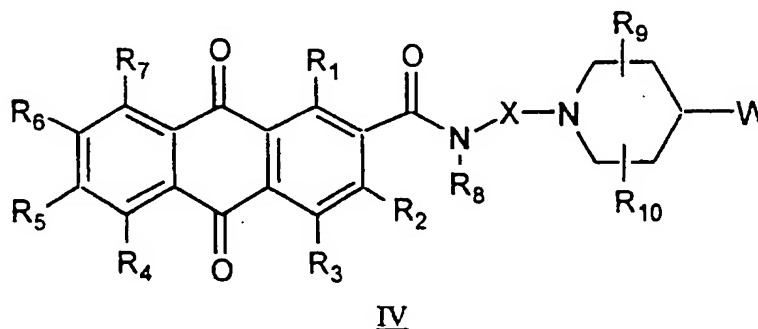
wherein R₈, X, and W are as defined above for Formula I.

Preferred compounds of formula IIIA include those where R₈ is hydrogen, methyl, or ethyl, and X is alkylene of 3-5 carbon atoms.

In other preferred compounds of Formula IIIA, R₈ is hydrogen and X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

More preferred compounds of Formula IIIA are those where R₈ is hydrogen; A is C₃-5 alkylene; and W is quinolinyl, isoquinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the group to the tetrahydropyridine ring), the groups being independently selected from chloro, methyl, and methoxy. Particularly preferred compounds of Formula IIIA are those where R₈ is are hydrogen; A is C₄ alkylene; and W is naphthyl, 8-quinolinyl, or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the tetrahydropyridine ring), the groups being independently selected from chloro, methyl, and methoxy.

Further, the invention provides compounds of Formula IV:

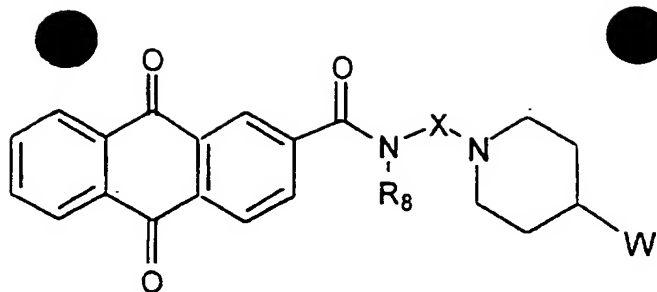


wherein R₁-R₁₀, X, and W are as defined above for Formula I.

Preferred compounds of formula IV include those where R₈ is hydrogen and X is alkylene of 3-5 carbon atoms. Particularly preferred compounds of Formula IV are those where R₈ is hydrogen, and X is butylene, i.e., C₄ alkylene.

In other preferred compounds of Formula IV, R₈ is hydrogen, X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

The invention also encompasses compounds of Formula IVA:

IVA

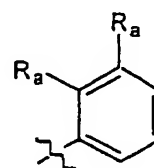
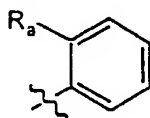
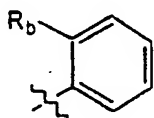
wherein R₈, X, and W are as defined above for Formula I.

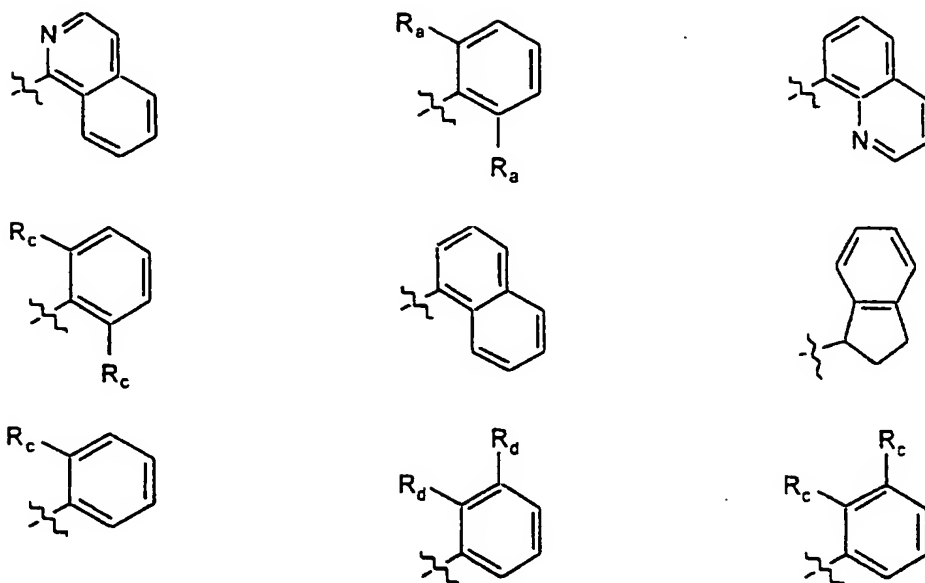
Preferred compounds of formula IVA include those where R₈ is hydrogen, methyl, or ethyl, and X is alkylene of 3-5 carbon atoms.

In other preferred compounds of Formula IVA, R₈ is hydrogen and X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

More preferred compounds of Formula IVA are those where R₈ is hydrogen; A is C₃-5 alkylene; and W is quinolinyl, isoquinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the group to the piperidine ring), the groups being independently selected from chloro, methyl, and methoxy. Particularly preferred compounds of Formula IVA are those where R₈ is hydrogen; A is C₄ alkylene; and W is naphthyl, 8-quinolinyl, or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the piperidine ring), the groups being independently selected from chloro, methyl, and methoxy.

Preferred compounds of the invention include W groups selected from the following:





In the above W groups, the following definitions apply:

R_a is halogen;

R_b represents alkoxy;

R_c represents alkyl;

R_d represents hydrogen, R_a or R_c .

In those formulas where more than one of the same substituent appears, those substituents are the same or different.

Particularly preferred W groups of the invention include 2-methoxyphenyl; 2,3-Dimethylphenyl; 1-Naphthyl; 1-Isoquinolyl; 1,2-Dihydroindanyl; 8-Quinoliny; 2-Chlorophenyl; 2,3-Dichlorophenyl; 2,6-Dimethylphenyl; 2,6-Dichlorophenyl; 2-Methyl-3-chlorophenyl; and 2-Methylphenyl.

When a compound of the invention is obtained as a mixture of enantiomers, these enantiomers may be separated, when desired, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Figure I and their pharmaceutically acceptable salts. The present invention also encompasses prodrugs, such as acylated prodrugs, of the compounds of Formula I. Those skilled in the art will recognize

various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and prodrugs of the compounds encompassed by Formula I.

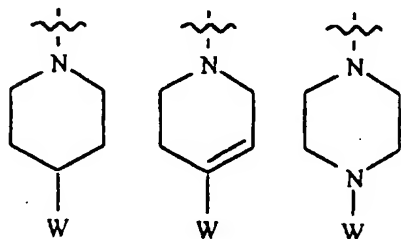
Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table 1 and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanolic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

By "alkyl" and "lower alkyl" is meant straight and branched chain alkyl groups having from 1-6 carbon atoms, e.g., C_1 - C_6 alkyl.

By "lower alkoxy" and "alkoxy" is meant straight and branched chain alkoxy groups having from 1-6 carbon atoms, e.g., C_1 - C_6 alkoxy.

By halogen is meant fluorine, chlorine, bromine and iodine.

The amino group represented by Y above includes groups represented by the formulas

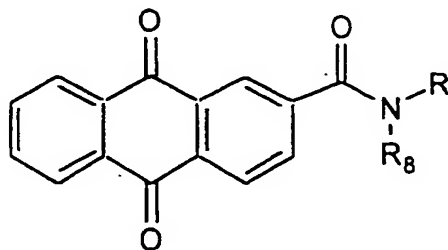


where W is defined above.

Particularly preferred W groups of the invention are dihydroindenyl, quinolinyl, isoquinolinyl, or phenyl, where phenyl is optionally substituted with up to two substituents independently selected from halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy. These optional phenyl substituents are preferably in the 2 and/or 3 positions of the phenyl group relative to the point of attachment of the phenyl group to the 6-membered nitrogen containing ring.

Representative examples of compounds according to the invention are shown in Table 1 below. The number below each compound is its compound number. Each of these compounds may be prepared according to the general reaction Scheme I set forth below.

Compounds 1-5 in Table 1 have the following general formula A:

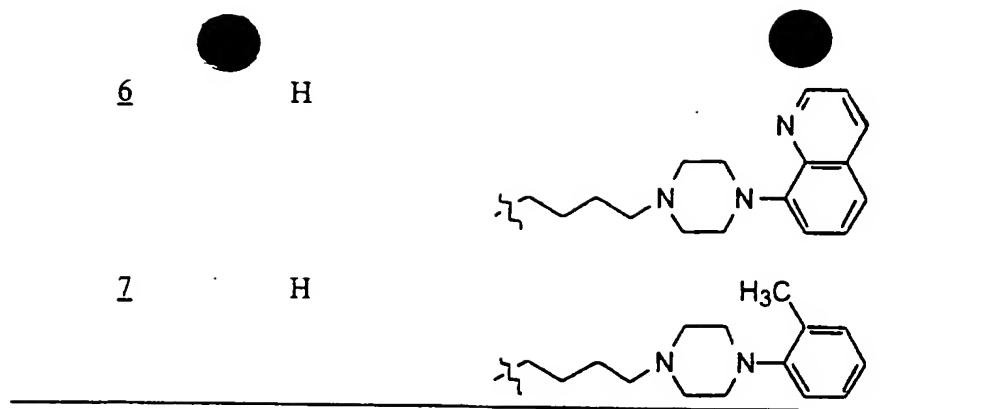


A

where R and R₈ are defined in the table.

Table 1

Compound Number	R ₈	R
<u>1</u>	H	
<u>2</u>	H	
<u>3</u>	H	
<u>4</u>	H	
<u>5</u>	H	



Particular compounds according to the invention include:

- 5 N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- 10 N-(1-{4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- N-(1-{4-[4-(2-Methyl-3-chlorophenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- 15 N-(1-{4-[4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- N-(1-{4-[4-(8-Quinoliny)]piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- 20 N-(1-{4-[4-(2-Methylphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride
- 25 N-(1-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride

The invention also pertains to the use of compounds of general Formula I in the treatment of neuropsychological disorders. The pharmaceutical utility of compounds of this invention are indicated by the following assays for dopamine receptor subtype affinity.

ASSAY FOR D₂ AND D₃ RECEPTOR BINDING ACTIVITY

Pellets of COS cells containing recombinantly produced D₂ or D₃ receptors from African Green monkey were used for the assays. The sample is homogenized in 100 volumes

(w/vol) of 0.05 M Tris HCl buffer at 4° C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 100 mM NaCl.

Incubations are carried out at 48°C and contain 0.4 ml of tissue sample, 0.5 nM ³H-YM 09151-2 and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 1 mM spiperone; without further additions, nonspecific binding is less than 20% of total binding. The binding characteristics of representative compounds of the invention for D₂ and D₃ receptor subtypes are shown in Table 2 for rat striatal homogenates.

TABLE 2

Compound Number ¹	D ₂ K _i (nM)	D ₃ K _i (nM)
1	154	4
4	61	2
6	45	2
7	106	1

¹ Compound numbers relate to compounds shown above in Table 1.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches,

lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more
5 sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and
10 flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents
15 and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may
20 be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the and partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be
25 formulated according to the known art using those suitable dispersing or wetting agents and

suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or
5 suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of
10 suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile
15 medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

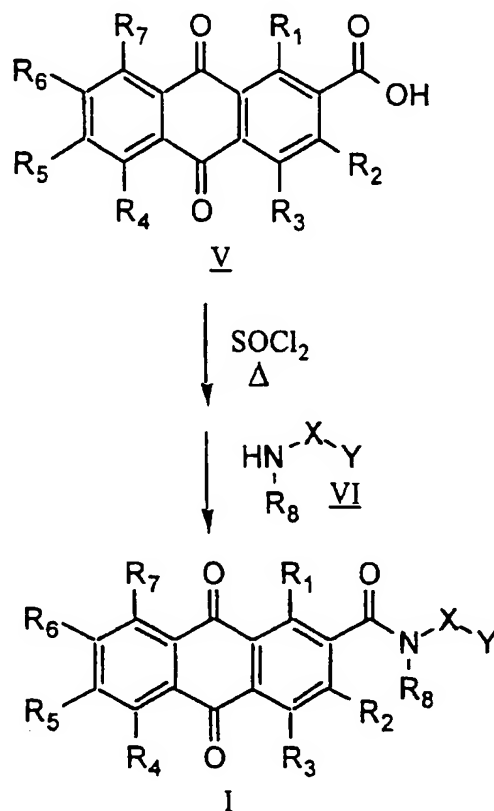
Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to
20 about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient
25 will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preparation of N-Aminoalkylantraquinonecarboxamides

The compounds of Formula I, and the pharmaceutically acceptable acid addition salts thereof, may be prepared according to the reactions shown below in Scheme 1.

Scheme 1



wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and X and Y are as defined above for Formula I.

As shown, a compound of Formula V may be activated by treating the acid V with an activating agent such as, for example, refluxing thionyl chloride (SOCl₂) or the like. The resulting activated species, e.g., an acyl chloride, may be subsequently reacted with the required compound of Formula VI at room temperature, optionally in a suitable solvent such as chloroform, to afford a compound of Formula I as the desired product.

Where they are not commercially available, the compounds of Formula V may be known procedures or by procedures analogous to those described in literature. The compounds of Formula VI are either known or capable of being prepared by various methods

known in the art. Example 1 below provides a representative preparation of a compound of Formula VI.

Those having skill in the art will recognize that the starting materials may be varied and/or additional steps employed as needed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. These examples illustrate the presently preferred methods for preparing the compounds of the invention.

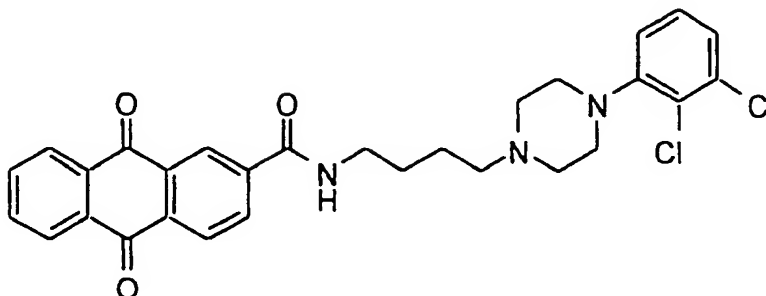
Example 1

1-(2-methoxyphenyl)-4-(4-aminobutyl)piperazine

Powdered potassium carbonate (22 g) was added to a solution of 1-(2-methoxyphenyl)piperazine (14 g, 0.073 mmol) and N-(4-bromobutyl)phthalimide (20 g, 0.070 mmol) in 200 mL of dimethylformamide and the resulting mixture was stirred and heated at 80 °C for 28 h. After cooling to room temperature the mixture was partitioned between water (500 ml) and diethyl ether (500 ml). The organic layer was further washed with two 200 mL portions of water, dried (Na₂SO₄) and concentrated. The resulting white solid was recrystallized from isopropanol to give 12 g of white crystals. The solid material was placed in hydrazine hydrate (150 mL) and heated to reflux under a nitrogen atmosphere. After 3 h the reaction was cooled and poured partitioned between water (400 mL) and diethyl ether (200 mL). Potassium carbonate (60 g) was added to the water layer and the resulting solution was extracted with methylene chloride (200 ml). The combined organic extracts were dried

(Na₂SO₄) and concentrated to give 1-(2-methoxyphenyl)-4-(4-aminobutyl)piperazine as a pale yellow oil (8.7 g).

Example 2



1. N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]}butyl)-
2-anthraquinonecarboxamide hydrochloride

2-Anthraquinonecarboxylic acid (100 mg, 0.45 mmol) was refluxed in 5 mL of thionyl chloride for 20 hours. After complete evaporation of the residual thionyl chloride under reduced pressure, a solution of 4-[4-(2,3-dichlorophenyl)piperazin-1-yl]-1-aminobutane (150 mg, 0.5 mmol) in 5 mL of chloroform was added followed by 1 g of triethylamine. The resulting mixture was stirred for 30 minutes. The reaction mixture was then partitioned between ethyl acetate and 10% aqueous NaOH. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give the title compound, Compound 1 (183 mg, 80%). The hydrochloride (mp 202-205 °C) salt was prepared by treating the free base with a mixture of diethyl ether-HCl.

Example 3

The following compounds are prepared essentially according to the procedures set forth above.

(a) N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride (mp 240-242 °C).

(b) N-(1-{4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride (mp 244-245 °C).

(c) N-(1-{4-[(2-Methyl-3-chlorophenyl)piperazin-1-yl]}butyl)-2-anthraquinone-carboxamide hydrochloride (mp 234-236 °C).

(d) N-(1-{4-[4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl]}butyl)-2-anthraquinone-carboxamide hydrochloride (mp 224-226 °C).

5 (e) N-(1-{4-[4-(8-Quinoliny)]piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride (mp 230-232 °C).

(f) N-(1-{4-[4-(2-Methylphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride (mp 243-244 °C).

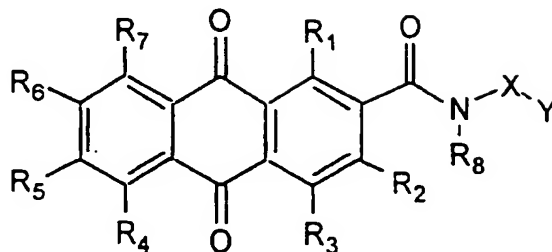
(g) N-(1-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride (mp 222-223 °C).

10

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it
15 pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

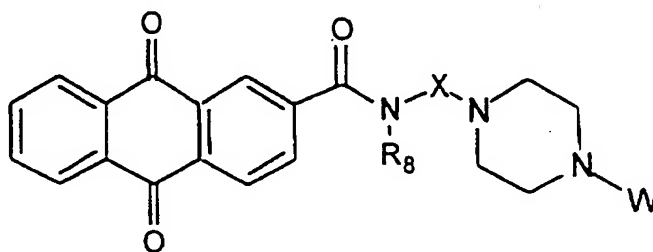
1. A compound of the formula:



or the pharmaceutically acceptable acid addition salts thereof wherein:

- 5 R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are the same or different and represent hydrogen, halogen, alkyl, alkoxy, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy; -O₂CR', -NHCOR', -COR', -SO_mR', where R' is C₁-C₆ alkyl and wherein m is 0, 1 or 2; or R₁, R₂, R₃, R₄, R₅, R₆, and R₇ independently represent -CONR'R'', or -NR'R'' where R' and R'' independently represent hydrogen or C₁-C₆ alkyl;
- 10 R₈ is hydrogen or lower alkyl;
- X represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more alkyl groups having from 1 to 4 carbon atoms;
- Y represents a cycloalkyl amino group.

15. 2. A compound of the formula:



wherein:

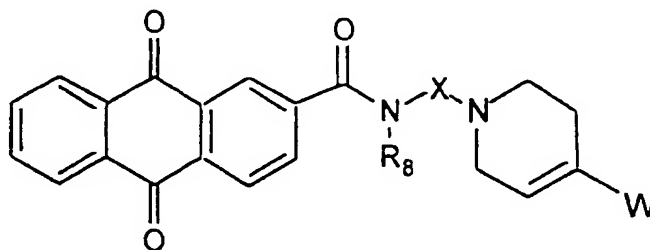
- R₈ is hydrogen or lower alkyl;
- X represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more alkyl groups having from 1 to 4 carbon atoms; and
- 20 W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl, dihydroindenyl, quinolinyl, pyridinyl, pyrimidyl, isoquinolinyl, benzofuranyl, or benzothienyl, each of which is optionally

substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

5 3. A compound according to Claim 2, wherein R₈ is hydrogen and X is alkylene of 3-5 carbon atoms.

10 4. A compound according to Claim 2, wherein R₈ is hydrogen, X is alkylene of 3-5 carbon atoms, and W is dihydroindenyl, quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

4. A compound of the formula:



15 wherein

R₈ is hydrogen or lower alkyl;

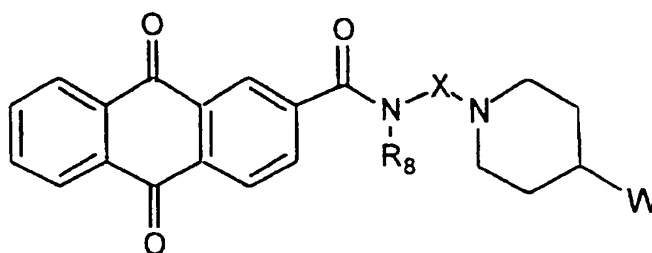
X represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more alkyl groups having from 1 to 4 carbon atoms; and

20 W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl, dihydroindenyl, quinolinyl, pyridinyl, pyrimidyl, isoquinolinyl, benzofuranyl, or benzothienyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

5. A compound according to Claim 4, wherein R₈ is hydrogen and X is alkylene of 3-5 carbon atoms.

6. A compound according to Claim 4, wherein R₈ is hydrogen, X is alkylene of 3-5 carbon atoms, and W is quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

7. A compound of the formula



wherein

R₈ is hydrogen or lower alkyl;

X represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more alkyl groups having from 1 to 4 carbon atoms; and

W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl, dihydroindenyl, quinolinyl, pyridinyl, pyrimidyl, isoquinolinyl, benzofuranyl, or benzothienyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

8. A compound according to Claim 7, wherein R₈ is hydrogen and X is alkylene of 3-5 carbon atoms.

9. A compound according to Claim 7, wherein R₈ is hydrogen, and X is butylene.

10. A compound according to Claim 7, wherein R₈ is hydrogen, X is alkylene of 3-5 carbon atoms, and W is quinolinyl, isoquinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, and hydroxy.

5

11. A compound according to Claim 10, wherein X is butylene.

12. A compound according to Claim 1, which is N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

10

13. A compound according to Claim 1, which is N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

15

14. A compound according to Claim 1, which is N-(1-{4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

15. A compound according to Claim 1, which is N-(1-{4-[4-(2-Methyl-3-chlorophenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

20

16. A compound according to Claim 1, which is N-(1-{4-[4-(8-Quolinyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

17. A compound according to Claim 1, which is N-(1-{4-[4-(2-Methylphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

25

18. A compound according to Claim 1, which is N-(1-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]}butyl)-2-anthraquinonecarboxamide hydrochloride.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/97/06162

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D295/12 C07D211/70 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 395 835 A (SHELLY A. GLASE ET AL) 7 March 1995 cited in the application see the whole document ---	1-18
A	GB 824 530 A (BASF AG) 2 December 1959 see the whole document ---	1-18
P,A	WO 97 10229 A (NEUROGEN CORPORATION) 20 March 1997 see the whole document -----	1-18

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

5 August 1997

Date of mailing of the international search report

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Luyten, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US97/06162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5395835 A	07-03-95	AU 1877495 A	09-10-95
		CA 2180155 A	28-09-95
		EP 0751939 A	08-01-97
		FI 963294 A	23-08-96
		HU 76058 A	30-06-97
		NO 963996 A	23-09-96
		PL 316313 A	06-01-97
		WO 9525727 A	28-09-95
		ZA 9502382 A	10-01-96

GB 824530 A		DE 1054959 B	
		FR 1190264 A	12-10-59

WO 9710229 A	20-03-97	AU 7019396 A	01-04-97

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